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APPLICATION FOR A PATENT AND
ACKNOWLEDGEMENT OF RECEIPT
(Section 30(1) Regulation 22)

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THE GRANT OF A PATENT IS HEREBY REQUESTED BY THE UNDERMENTIONED APPLICANT ON THE BASIS OF THE PRESENT APPLICATION FILED IN DUPLICATE

REGISTRATEUR VAN SUID AFRIKA

21	01	PATENT APPLICATION NO	974806	A&A REF: SA 136093

71 FULL NAME(S) OF APPLICANT(S)

ABBOTT LABORATORIES

ADDRESS(ES) OF APPLICANT(S)

100 ABBOTT PARK ROAD
ABBOTT PARK
ILLINOIS 60064-3500
U.S.A.

54 TITLE OF INVENTION

PROSTAGLANDIN SYNTHASE-2 INHIBITOR

Only the items marked with an "X" in the blocks below are applicable.

[X] THE APPLICANT CLAIMS PRIORITY AS SET OUT ON THE ACCOMPANYING FORM P.2. The earliest priority claimed is
Country: US No: 08/667,781 Date: 21 JUNE 1996

[ ] THE APPLICATION IS FOR A PATENT OF ADDITION TO PATENT APPLICATION NO 21 01

[ ] THIS APPLICATION IS A FRESH APPLICATION IN TERMS OF SECTION 37 AND BASED ON APPLICATION NO 21 01

THIS APPLICATION IS ACCOMPANIED BY:

- [X] Two copies of a complete specification of 13 pages
- [X] Drawings of 2 sheets
- [ ] Publication particulars and abstract (Form P.8 in duplicate) (for complete only)
- [ ] A copy of Figure of the drawings (if any) for the abstract (for complete only)
- [X] An assignment of invention
- [ ] Certified priority document(s). (State quantity)
- [ ] Translation of the priority document(s)
- [ ] An assignment of priority rights
- [ ] A copy of Form P.2 and the specification of RSA Patent Application No 21 01
- [X] Form P.2 in duplicate
- [X] A declaration and power of attorney on Form P.3
- [ ] Request for ante-dating on Form P.4
- [ ] Request for classification on Form P.9
- [ ] Request for delay of acceptance on Form P.4
- [ ] Extra copy of informal drawings (for complete only)

74 ADDRESS FOR SERVICE: Adams & Adams, Pretoria

Dated 30 MAY 1997

ADAMS & ADAMS
APPLICANTS PATENT ATTORNEYS

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PATENT ATTORNEYS
PRETORIA

FORM P7

REPUBLIC OF SOUTH AFRICA
Patents Act, 1978

COMPLETE SPECIFICATION

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71	FULL NAME(S) OF APPLICANT(S)

ABBOTT LABORATORIES

72	FULL NAME(S) OF INVENTOR(S)

JOSEPH F. DELLARIA, JR.
TODD H. GANE
KEITH W. WOODS

54	TITLE OF INVENTION

PROSTAGLANDIN SYNTHASE-2 INHIBITOR

PROSTAGLANDIN SYNTHASE-2 INHIBITOR

Technical Field

The present invention relates to an organic compound having biological activity, to pharmaceutical formulations containing that compound, and to medical methods of treatment. More particularly, this invention concerns the compound *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide, pharmaceutical compositions and a method of using the compound to treat inflammatory disease states.

Background

Prostaglandins are chemical mediators involved in the process of cell to cell signaling. These molecules belong to a general class of compounds called prostanoids which are compounds derived from C_{20} fatty acids. Prostaglandins are continuously synthesized in cell membranes from precursors cleaved from membrane phospholipids by phospholipases. (Molecular Biology of the Cell, 2nd ed. 1989). Phopholipases act upon membrane phospholipids to cause the release of arachidonic acid, which is then acted upon by the enzyme prostaglandin synthase (PGS) in forming the precursor molecules of prostaglandins.

PGS has two distinct activities which catalyze two sequential biochemical reactions *in vivo*. The first activity, mediated by the enzyme cyclooxygenase (COX), converts free arachidonic acid to an unstable intermediate, prostaglandin G_2 (PGG_2). The hydroperoxidase activity of PGS then converts PGG_2 to a common precursor known as PGH_2. PGH_2 is acted upon by various synthases to produce bioactive prostanoids such as prostaglandins (PGE, PGF etc.) thromboxanes, and prostacyclins. (Herschman, H.R., *Biochimica et Biophysica Acta*, **1299:** 125-140 (1996)).

For many years, the rate-limiting step in the production of the prostanoids in response to cellular stimulation was thought to be the activation of phospholipase(s) to release membrane-bound arachidonic acid. It was also believed that constitutive levels of PGS were present (in excess) in cells and available to convert free arachidonic acid to PGH_2. Recently however, a gene was identified that expresses a second, inducible form of PGS, referred to as PGS-2 or COX-2. Both isoforms (PGS-1 or COX-1, which is constitutively expressed) and COX-2 play a central role in prostaglandin synthesis.

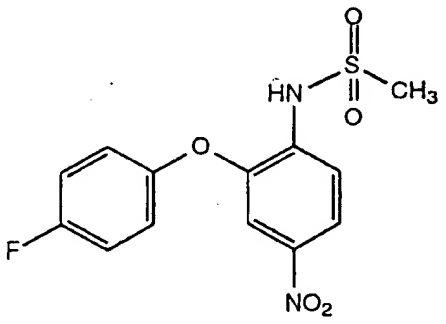
Despite their common role, COX-1 and COX-2 differ in several ways, including structure, regulation and tissue distribution. COX-1 for example, is constitutively expressed and is assumed to be responsible for producing prostanoids for physiological functions. In contrast, COX-2 appears to be expressed only by specific inflammatory stimuli and is down-regulated by glucocorticoids. (Simmons, et al., *J Lipid Med*, **6:** 113-117 (1993)). This has led to the hypothesis that a highly expressed COX-2 is responsible for the high levels of prostanoids present in inflamed tissues. (Klein, T. *et al.*, *Biochemical Pharmacology*, 48(8): 1605-1610 (1994). It has also been proposed that compounds which inhibit COX-2 may

eleviate or reduce pathological conditions associated with prostaglandin production. (*Op. cit.*)

One class of compounds shown to be useful in inhibiting cyclooxygenase are non-steroidal anti-inflammatory drugs (NSAIDs) which include such commercially available compounds as aspirin, ibuprofen and naproxen. NSAIDs however, share a common side effect of gastric distress rationalized as due to inhibition of constitutive COX-1 in the gastric mucosa. (Allison, M. C. *et al., N. Engl. J. Med.* 327: 749-754 (1993)). Several new compounds have been developed that appear to have a better side effect profile. For example, substituted 2-phenoxy sulfonanilides having anti-inflammatory activity have been described in U.S. Patent No. 3,840,597 to Riker *et al.*. Other compounds, also having this advantageous effect, have been shown to be selective inhibitors of COX-2. There is a continuing need for therapeutically effective NSAIDs which selectively inhibit COX-2 activity and reduce the side effects associated with the use of current NSAIDs.

Summary of the Invention

The present invention provides a selective inhibitor of the enzyme cyclooxygenase-2 (COX-2). This inhibitor, chemically referred to as *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide is a compound having the formula:



In another aspect, the present invention provides a pharmaceutical composition for inhibiting COX-2 comprising a pharmaceutical carrier and a therapeutically effective amount of the compound of the invention.

In another aspect, the present invention provides a method for inhibiting COX-2 in a patient in need of such treatment comprising administering a therapeutically effective amount of the compound of the invention.

In yet another aspect, the present invention provides therapeutic methods and in particular, for treating a patient in need of anti-inflammatory, analgesic and anti-pyretic therapy.

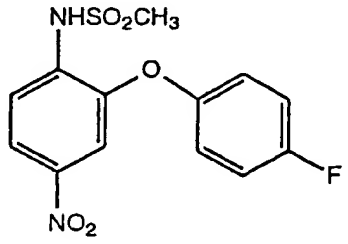
Brief Description of the Drawings

FIG. 1 shows a graph of the plasma drug concentrations over time of *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide (represented by the dotted line) and nimesulide (represented by the solid line) in dogs.

FIG. 2 shows the plasma drug concentrations over time of *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide (represented by the dotted line) and nimesulide (represented by the solid line) in rats.

Detailed Description of the Invention

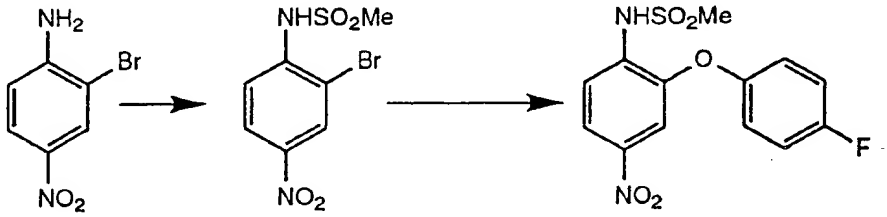
In accordance with the present invention is the compound *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide having the formula:



As will be shown below, this compound is a selective inhibitor of COX-2 activity.

N-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide can be prepared as shown in Scheme I. Intermediate I (which is commercially available) can be reacted using standard reagents and methods for effecting a sulfonylation reaction, for example, with a solvent such as DMF and in the presence of a base. Subsequent acidification with an acid such as citric acid and extraction with a solvent such as ethyl acetate produces Intermediate II. Intermediate II is then reacted with a solution of 4-fluorophenol, a base and a copper halide (i.e. via Ullmann ether synthesis) to give the compound of the invention.

SCHEME 1



Intermediate I Intermediate II

The following example will serve to further illustrate the preparation of this compound.

EXAMPLE 1

Preparation of *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide

A. *N*-(4-Nitro-2-bromophenyl)-methanesulfonamide: *N*-(4-Nitro-2-bromophenyl)-methanesulfonamide was prepared by dissolving the commercially available 2-bromo-4-nitroaniline (10.0 g, 46.07 mmol) in DMF (250 mL) and adding NaH (60 % in oil dispersion; 3.7 g, 92.15 mmol) portion wise at 0 °C. After 15 minutes the methanesulfonyl chloride (10.7 mL, 138.23 mmol) was added and the reaction was allowed to stir overnight at room temperature. The reaction was acidified with 1M citric acid (100 mL) and extracted with ethyl acetate (3X). The combined extracts were washed with brine (2X), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a red oil that was purified by flash chromatography (silica gel; 20 % EtOAc/Hexane) to afford the desired product (3.2 g, 24 % yield) as a yellow solid which was recrystallyzed from ether/hexanes. mp 148-151 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.24 (s, 3H), 7.70 (d; J = 9 Hz; 1H), 8.23 (dd; J = 9, 3 Hz; 1H), 8.49 (d; J = 3 Hz; 1H), 9.85 (br. s., 1H). MS (DCI-NH_3) m/z 312 $(M+NH_4)^+$.

B. *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide: To a solution of 4-fluorophenol (400μL, 3.40 mmol), K_2CO_3 (470 mg, 3.40 mmol), and CuI (325 mg, 1.70 mmol), in DMF (20 mL) at room temperature was added *N*-(4-Nitro-2-bromophenyl)methanesulfonamide (1.0 g, 3.40 mmol). The reaction was heated at reflux for 5 hours and allowed to cool to room temperature. The reaction was acidified with 10 % HCl (aq) and extracted into EtOAc (3X). The combined extracts were washed with H_2O (2X), brine (2X), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown solid that was purified by flash chromatography (silica gel; 20 % EtOAc/Hexane) to afford the desired product (235 mg, 21 % yield) as a white solid which was recrystallyzed from ether/hexanes. mp 179-181 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20 (s, 3H), 7.20-7.37 (m, 4H), 7.52 (d; J = 3 Hz; 1H), 7.72 (d; J = 9 Hz; 1H), 8.04 (dd; J = 9, 3 Hz; 1H), 10.18 (br.s ., 1H). MS (DCI-NH_3) m/z 344 $(M+NH_4)^+$. Analysis Calc'd for $C_{13}H_{11}FN_2O_5S$: C, 47.85; H, 3.37; N, 8.58. Found: C, 47.94; H, 3.37; N, 8.46.

The compound of the invention is a selective inhibitor of COX-2. As a COX-2 inhibitor, the compound is useful in the treatment of conditions which are mediated by COX-2 activity. More particularly, the compound is useful for treating or modulating pathological conditions which are associated with the production of prostaglandins by COX-2. Thus, the compound is useful as an anti-inflammatory agent for treating both acute inflammatory conditions (such as those resulting from infection) and chronic inflammatory conditions (such as those resulting from asthma, arthritis and inflammatory bowel disease). It is also useful as

an analgesic and anti-pyretic agent (i.e. for reducing pain and fever). Further uses are for the prevention of cardiovascular disease, the prevention of bone resorption and for the reduction of colon cancer.

When used in the above or other treatments, a therapeutically effective amount of the compound of the present invention may be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt form. By a "therapeutically effective amount" of the compound of the invention is meant a sufficient amount of the compound to inhibit COX-2 activity,at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compound and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed, the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The total daily dose of the compounds of this invention administered to a human may range from about 0.1 to about 500 mg/kg of patients body mass/day. For purposes of oral administration, more preferable doses may be in the range of from about 0.1 to about 100 mg/kg/day. If desired, the effective daily dose may be divided into multiple doses for purposes of administration; consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

In the pharmaceutical compositions of the present invention, a compound of the invention is combined with a pharmaceutically acceptable carrier or excipient, meaning a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The compositions may be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, drops or transdermal patch), bucally, or as an oral or nasal spray. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically-acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable

solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption, such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations may be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically-acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain

silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules may be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Liquid dosage forms for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions may contain, in addition to the active compounds, suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

Topical administration includes administration to the skin or mucosa, including surfaces of the lung and eye. Compositions for topical administration, including those for inhalation, may be prepared as a dry powder which may be pressurized or non-pressurized. In non-pressurized powder compositions, the active ingredient in finely divided form may be used in admixture with a larger-sized pharmaceutically-acceptable inert carrier comprising particles having a size, for example, of up to 100 micrometers in diameter. Suitable inert carriers include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

Alternatively, the composition may be pressurized and contain a compressed gas, such as nitrogen or a liquefied gas propellant. The liquefied propellant medium and indeed the total composition is preferably such that the active ingredient does not dissolve therein to any substantial extent. The pressurized composition may also contain a surface active agent, such as a liquid or solid non-ionic surface active agent or may be a solid anionic surface active agent. It is preferred to use the solid anionic surface active agent in the form of a sodium salt.

A further form of topical administration is to the eye as for the treatment of inflammatory conditions. The compound of the invention is delivered in a pharmaceutically acceptable ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, as for example the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/cilary, lens, choroid/retina and sclera. The pharmaceutically-acceptable ophthalmic vehicle may, for example, be an ointment, vegetable oil or an encapsulating material.

Compositions for rectal or vaginal administration are preferably suppositories which may be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention may also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically-acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*

The selectivity of the compound *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide for COX-2 is illustrated by the following data.

Selective Inhibition of COX-2 by *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide

I. Methodologies

A. Enzymatic Assay: Compounds 1, 2 and 3 (corresponding to nimesulide, 4-nitro-2-

phenoxytrifluoromethanesulfonanilide, and *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide respectively) were dissolved in DMSO (3.3% v/v) and preincubated with recombinant human COX-1 or COX-2 (rHuCOX-1, rHuCOX-2, supplied by Abbott Laboratories), together with the cofactors phenol (2 mM) and hematin (1 μM) for 60 minutes prior to the addition of 10 μM arachidonic acid. The time of preincubation of the enzymes with each compound was 60 minutes. The reaction was allowed to run for 2.5 minutes at room temperature prior to quenching with HCl and neutralization with NaOH. PGE_2 production in the presence and absence of drug was determined by enzyme immunoassay (EIA) analysis as described below. Results from control incubations were compared to drug treated samples and per cent inhibition values were calculated. IC_{50}'s were calculated from concentration response curves.

B. EIA Assay: EIA reagents for prostaglandin determination were purchased from Perseptive Diagnostics, Cambridge, MA. PGE_2 levels in enzyme assays were determined after samples were dried under nitrogen and reconstituted with assay buffer and were measured against standards prepared under the same conditions. Immunoassays were conducted as recommended by the manufacturer. Optical density was measured using a Vmax microplate reader purchased from Molecular Devices Corp., Menlo Park, CA.

II. Results

When tested in the manner described above, all three compounds were shown to be potent inhibitors of rHuCOX-2, with compound 2 being most potent. Based on confidence limits (% C.L.) of the calculated IC_{50}s, compounds 1 and 3 were shown to be more selective inhibitors of rHuCOX-2 than was compound 2 (see Table 1).

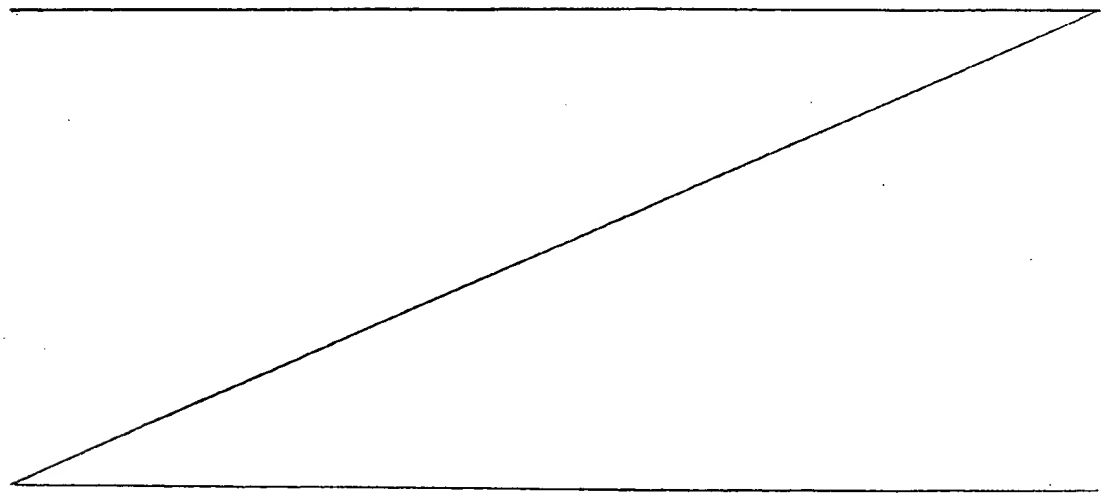


Table 1

Compound*	rHuCOX-2 IC_{50} nM (95% C.L.)	rHuCOX-2 IC_{50} µM (95% C.L.)	rHuCOX-1 / rHuCOX-2
1	16 (4-29)	59 (9-103)	3,700
2	0.10 (0.08-0.13)	0.06 (0.02-0.14)	600
3	13 (7-20)	28 (20-39)	2,200

* Compound 1 = nimesulide; Compound 2 = *N*-[4-Nitro-2-phenoxy phenyl]trifluromethane sulfonamide; Compound 3 = *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide

The slower rate at which the compound of the invention is metabolized *in vivo* is illustrated by the following data.

Comparative Pharmacokinetics of N-[4-Nitro-2-phenoxy phenyl]trifluromethane sulfonamide and Nimesulide

I. Methodologies:

A. Dog and Rat Pharmacokinetics: Experiments were performed *in vivo* to compare the terminal half-life ($t_{1/2}$) of *N*-[4-Nitro-2-(4'-fluorophenoxy)phenyl]methanesulfonamide with that of its unsubstituted parent, nimesulide (SIGMA Chemical Co., St. Louis, MO). "Terminal half-life" refers to the time period in which 50% of a compound is cleared from the blood (following the distributive phase from dosing). Experiments were performed on dogs in the following manner: Three fasted beagles were intravenously administered a single dose of both nimesulide and *N*-[4-Nitro-2-(4'-fluorophenoxy)phenyl]methanesulfonamide at 2 µmoles/kg in the same dose solution. Serial blood samples of 0.5 mL were taken over an 8 hour time period, centrifuged and the resulting plasma fraction processed for HPLC in the manner described below. A 76-hr sample was subsequently obtained when it was observed that the 8 hr. samples had significant drug levels.

For the rats, conscious Sprague-Dawley rats having chronic venous (for dosing) and arterial (for sampling) cannulas were intravenously administered a single dose solution containing both nimesulide and *N*-[4-Nitro-2-(4'-fluorophenoxy)phenyl]methane-sulfonamide, each at a concentration of 2 µmoles/kg. Serial blood samples of 0.5 mL were taken over a 48 hour time period. Plasma was immediately isolated by centrifugation and held frozen until assayed by HPLC.

B. Sample Extraction and HPLC: To a plastic bullet containing 0.2 mL acetonitrile was added 0.1 mL of plasma sample or standard with rapid mixing for 5 seconds. Samples were centrifuged and 0.15 mL of the supernatant was transferred to a micro HPLC sample

vial containing 0.15 mL water. Vials were capped, mixed and 50 µL injected onto the HPLC column.

A reverse-phase YMC Basic ODS column (25 x 0.46 cm) was used with a mobile phase of CH_3CN/tetramethylammonium perchlorate (0.01M)-trifluoroacetic acid (0.1%) in 10mM potassium phosphate (38:62) and adjusted to pH 8.1. Flow rate was 1.2 mL/min. with detection at 395 nm. retention times were about 6 min. for nimesulide and 6.8 min. for 2-(4'-fluoro-phenoxy)-4-nitro-sulfonanilide.

II. Results:

FIG. 1 and FIG. 2 show the plasma drug concentration vs. time profiles for nimesulide and *N*-[4-Nitro-2-(4'-fluorophenoxy)phenyl]methanesulfonamide administered to dogs and rats. In dogs (FIG. 1), a rapid decline (distribution) in plasma levels was followed by a second peak and then a plateau. Secondary peaks which follow intravenous dosing are usually attributable to enterohepatic recycling of drug. Due to the secondary peaks, conventional pharmacokinetic analysis could not be easily performed. Instead, an estimate of the plasma half-life of each compound was determined using the terminal time points which, in the case of *N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide, included the average of time points obtained at 76 hours (= 11µM). In contrast, nimesulide was not detected in dog plasma at 76 hours.

In rats (see FIG. 2), a possible plateau for both compounds was suggested from the mean plasma concentration profiles, although these plateaus were not as evident as in dogs. Pharmacokinetic analysis indicated a significant $t_{1/2}$ difference between nimesulide and *N*-[4-Nitro-2-(4'-fluorophenoxy)phenyl]methanesulfonamide. The plasma half-live of both compounds in dogs and in rats is summarized in Table 2.

Table 2

	Half-life ($t_{1/2}$, hours)	
	Nimesulide	*N*-[4-Nitro-2-(4'-fluorophenoxy)-phenyl]methanesulfonamide
Dog (n=3)	8.90 ± 0.96	13.80 ± 0.60
Rat (n=3)	6.95 ± 0.12	15.34 ± 0.64

These results indicate that *para*-fluorination of nimesulide reduces its elimination rate by about 35% in dogs and 55% in rats. As a result of the slower elimination rates, higher blood drug levels of the compound are maintained over time which may allow for lower and/or less frequent dosing of *N*-[4-Nitro-2-(4'-fluorophenoxy)phenyl]methanesulfonamide.

Claims:

1. A compound which is *N*-[4-Nitro-2-(4'-fluorophenoxy)phenyl]methanesulfonamide.

2. A pharmaceutical composition for inhibiting COX-2 comprising a pharmaceutical carrier and a therapeutically effective amount of the compound of Claim 1.

3. A method for inhibiting COX-2 comprising administering to a human an effective amount of the compound of Claim 1.

4. A substance or composition for use in a method for treating a patient in need of anti-inflammatory therapy, said substance or composition comprising a compound of Claim 1, and said method comprising administering a therapeutically effective amount of said substance or composition.

5. A substance or composition for use in a method for treating a patient in need of analgesic therapy, said substance or composition comprising a compound of Claim 1, and said method comprising administering a therapeutically effective amount of said substance or composition.

6. A substance or composition for use in a method for treating a patient in need of anti-pyretic therapy, said substance or composition comprising a compound of Claim 1, and said method comprising administering a therapeutically effective amount of said substance or composition.

7. A substance or composition for use in a method for inhibiting COX-2, said substance or composition comprising a compound of Claim 1, and said method comprising administering to a human, a therapeutically effective amount of said substance or composition.

8. Use of a compound of Claim 1 in the manufacture of a medicament to inhibit COX-2 or to treat a patient in need of anti-inflammatory, analgesic or anti-pyretic therapy.

9. A pharmaceutical composition of Claim 1, substantially as herein described and illustrated.

10. A method of Claim 3, substantially as herein described and illustrated.

11. Use as claimed in Claim 8, substantially as herein described and illustrated.

12. A substance or composition for use in a method of treatment as claimed in any one of Claims 4 - 7, substantially as herein described and illustrated.

13. A new compound, new pharmaceutical composition, new non-therapeutic method of treatment, new use of a compound of Claim 1, or a substance or composition for a new use in a method of treatment, substantially as herein described.

DATED THIS 30TH DAY OF MAY 1997

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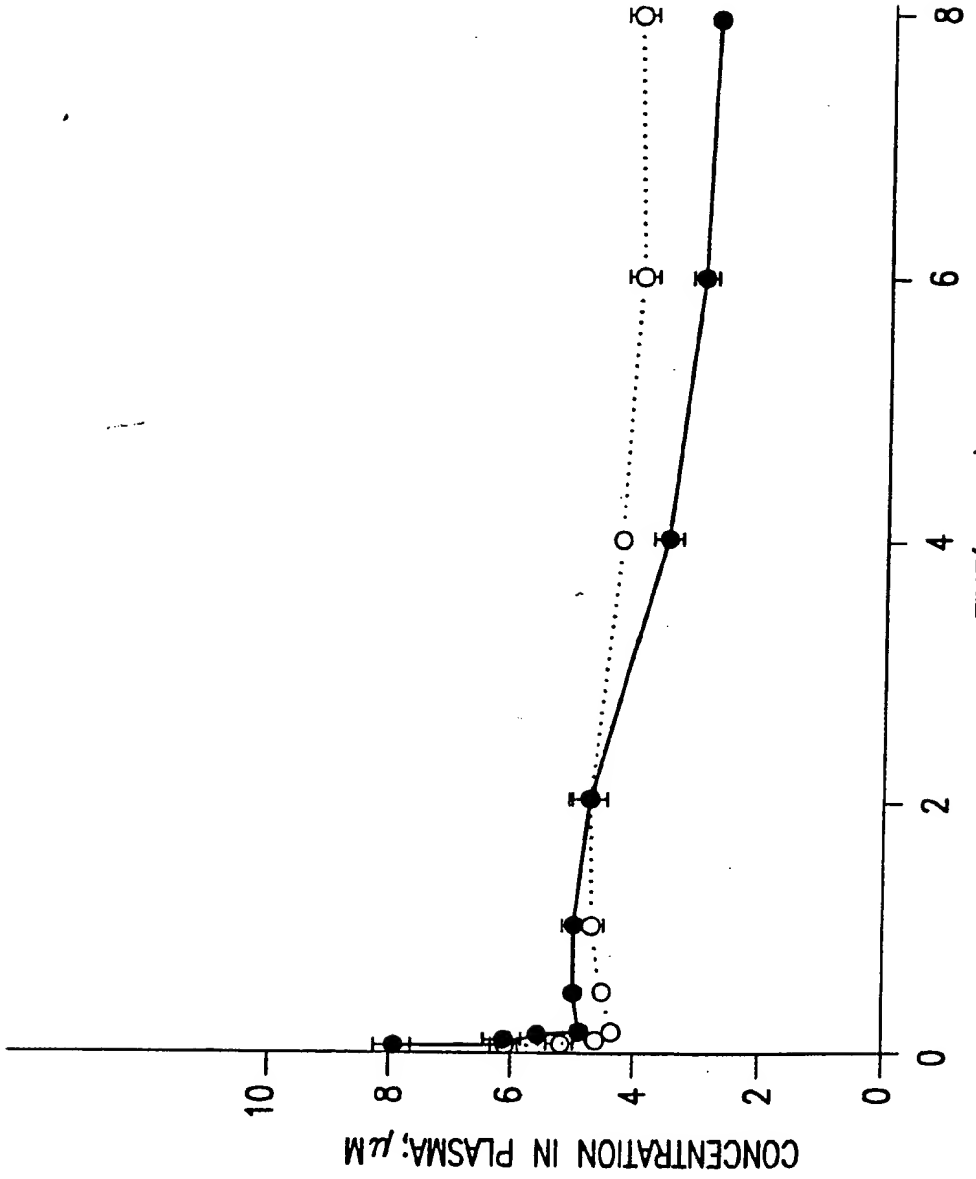

FIG.1

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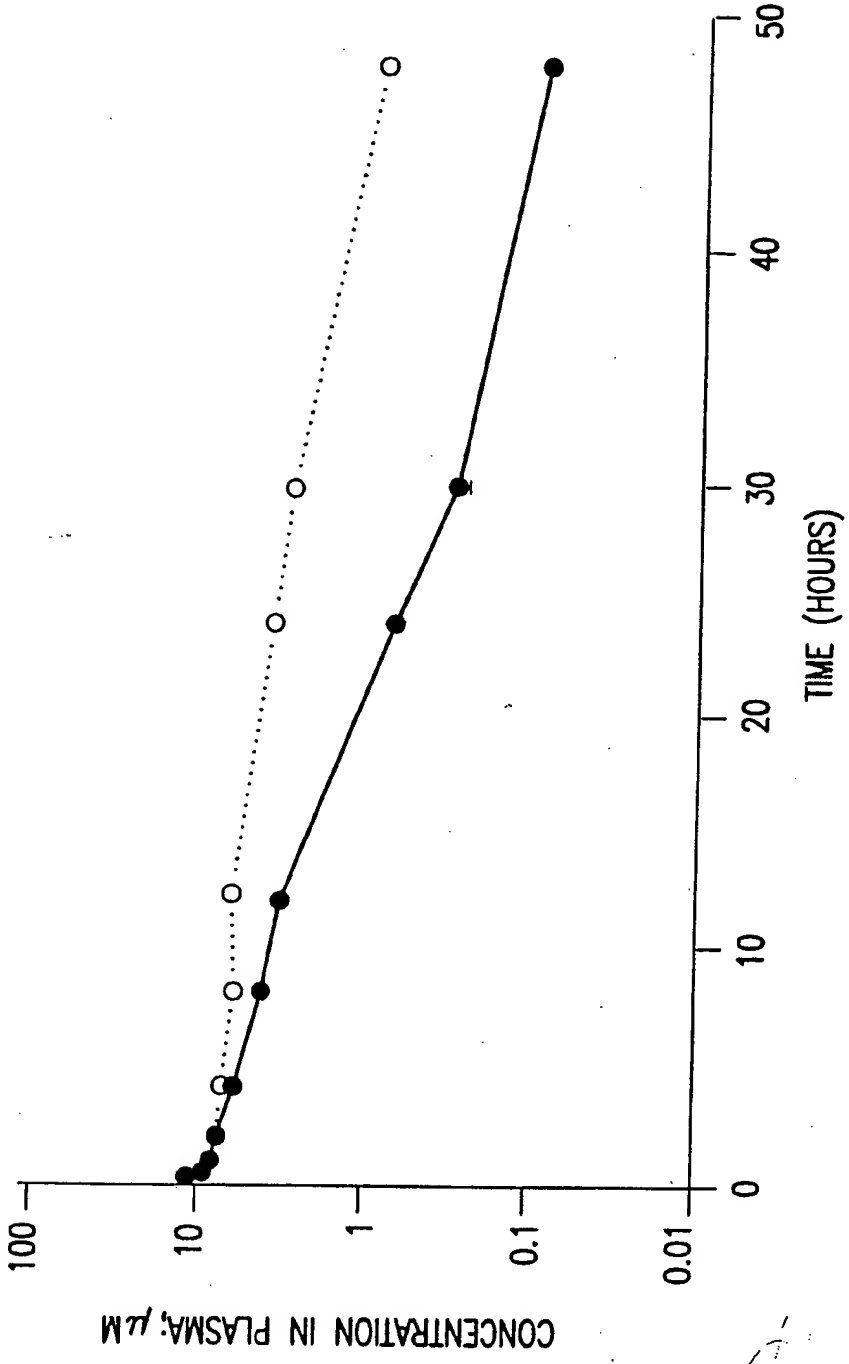

FIG.2

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